INFLUENZA EPIDEMICS AND THE INFLUENZA VIRUSES

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LECTURE II

In my first lecture I attempted to outline the history of influenza epidemics in this country in recent years and to describe the characteristics of the human disease invoked by the influenza viruses. In the present lecture I wish to refer mainly to the study of immunity to the viruses under natural or experimental conditions and to the development of possible methods of control of influenza.

Immunity to Influenza Virus Infection

From the earliest days of work with influenza virus in the laboratory the subject of immunity and of artificial methods of producing resistance to infection has been given constant attention. Much has been learnt; much probably remains undiscovered. The ability to control conditions and to standardize procedure in the laboratory has resulted in the accumulation of a valuable body of knowledge of immunity in experimental animals, much of which is probably applicable to the more complex immunity in man. Most of this work has been carried out on virus A, but there is no reason to suppose the results do not apply to virus B also. More recently, however, experiments on human volunteers have been carried out, with the result that knowledge concerning the duration of immunity and the effectiveness of various methods of immunization in man is accumulating rapidly.

Immunity in Experimental Animals

Ferrets are especially suitable for studies of immunity because of the resemblance between the infection induced by the viruses in this species and that occurring in man. Immediately after an attack of the disease the ferret is completely immune to reinfection, antibodies are present in high titre in the serum, and the immunity is broad-based so that heterologous strains of the same major type are resisted in addition to the homologous one. There is even, in the days of early convalescence, a cross-immunity between swine influenza virus and virus A, though not between virus B and virus A. Heterologous cross-immunity of this type may be present, though antibodies to the heterologous strain may not be detected in the serum. As time passes the homologous antibody level begins to fall and susceptibility to reinfection returns. However, homologous antibodies are still demonstrable in the serum when reinfection is possible, and the second attack, though accompanied by fever and nasal symptoms, is usually less severe and is not followed by the development of lung lesions if a lung-adapted strain of virus is used for the reinoculation.

In an attempt to illuminate the apparent failure of antibodies —that is, of humoral immunity—to explain the phenomena observed in the ferret, Francis and I (1938a, 1938b, 1938c) studied the histological changes in the nasal mucosa following primary inoculation and reinoculation with virus A. We found that a cycle of events occurs in the respiratory portion of the nasal mucosa during primary infection. The ciliated epithelium undergoes complete necrosis, leaving only a single basal layer of flattened cells, and, after three days, repair by growth of a many-layered pseudo-stratified type of epithelium sets in. Ciliated epithelium is not re-formed until a fortnight to three weeks after infection, but by the fourth week the damage to the epithelium has been largely repaired. The stratified epithelium present for several days during convalescence interested us very much, and we were able to show that this modification of the normal nasal mucosa, which is present when immunity is at its height, is resistant not only to reinoculation of virus but to unrelated physico-chemical agents. Zinc iontophoresis or simple instillation of zinc sulphate intranasally in normal ferrets produced an acute necrosis of the epithelium very similar to that of influenza, and repair and regeneration followed a similar course. The ferret convalescent from influenza showed, in the second week, a complete resistance of the nasal mucosa to destruction by iontophoresis, and the epithelium revealed no histological changes after this operation. As the epithelium of the convalescent animal became more normal, destruction by ionization again became possible, until at four weeks a normal reaction was obtained. The converse experiment of ionization of the nose followed by instillation of virus gave, however, no evidence of resistance by the regenerating epithelium to the virus.

These studies demonstrated to us that virus infection was followed by morphological changes, which were of a temporary character only and were therefore inadequate by themselves to explain the observed immunological phenomena. There seemed to us to be an analogy to the experiments of MacNider (1937) on the morphological changes of fixed tissue cells in the liver and kidney resulting from damage by chemicals. Whereas chemical tolerance to those agents was found by MacNider to be accompanied by a permanent modification of the liver and kidney structure, our abnormal nasal epithelium, on the other hand, was only transitory, and with the reappearance of a normal epithelium the non-specific resistance to damage was lost.

The nasal mucosa of ferrets exposed to reinfection at a time when immunity from the first infection had waned underwent necrotic changes similar to those seen in the first attack. Differences were discerned, however. Areas of epithelium sometimes remained normal, so that the necrosis tended to be focal in type, a more rapid repair followed the necrosis, and often the epithelium was not reduced to a single basal layer by the reinfection. This appeared to indicate a conditioning of the nasal mucosa by the first attack, so that the infecting agent was more readily repulsed and the damage more speedily repaired. Furthermore, if the ferret had had two previous nasal infections a solid immunity to a third or fourth inoculation might be encountered and then the nasal mucosa showed no histological changes at all. We studied the antibody levels of some of these ferrets prior to reinoculation, and were led to believe that the actual titre of circulating antibodies at the time of the immunity test was of fundamental importance.

These studies also afforded some explanation of the reaction observed in the ferret after subcutaneous inoculation with the virus. It has already been mentioned that infection does not follow introduction of virus by this route, and though antibodies subsequently develop in the serum the animal is not immune to nasal instillation of the virus, though possibly resistant to the more delicate test of contact infection (Smith, Andrewes, and Stuart-Harris, 1938). If parenteral inoculation of virus is given to a ferret in a state of waned immunity following an actual attack, the immunity may be boosted once more and a solid resistance to a second intranasal inoculation of virus may result. The production of a state of immunity by the re-installation of a high antibody level in an animal whose nasal mucosa is conditioned by previous infection can be readily visualized. Also from experiments on the immunization of ferrets, Francis (1939) was able to show that a considerable quantitative relationship existed between the degree of immunity following subcutaneous vaccination, the level of circulating antibodies at the time of the immunity test, and the amount of virus which was given in the vaccinating dose. Artificial immunization in the ferret is thus dependent for its success on the amount of actual virus antigen which is introduced parenterally; but the susceptibility of the nasal mucosa to infection, aided perhaps by the remoteness of the epithelium from circulating antibody in the serum, makes it impossible to reproduce the complete immunity which follows nasal infection.

Immunity in mice appears to be less complicated than that in ferrets, and it is also easier to produce a state of complete immunity by artificial immunization. The changes in the lung following intranasal inoculation with virus A have been studied by Oakley and Warrack (1940) and correlated with the presence of antibodies in the serum. The production of actual lung lesions was found to be essential with mouse-adapted strains of influenza virus for the subsequent development both of antibody and of immunity. Immunity developing after intranasal infection was broad-based, and was effective against heterologous virus A strains even in the absence of good levels of antibody against such strains. Other observers have found it to be possible to obtain immunity after intranasal infection

of mice in the absence of lung lesions, but only, however, if the virus used is not of mouse origin. Thus Burnet and Clark (1942) showed that unadapted human virus would both immunize and produce antibodies even though no lung lesions were produced, and Eaton and Beck (1940) obtained immunity without lung lesions by using ferret virus or tissue culture from chick embryos.

Because mouse-passage strains of virus must be used in high dilution if the production of lung lesions is to be avoided, it seems that these results simply mean that the effectiveness of immunity after actual infection in mice is closely dependent on the quantity of virus which has actually been administered. The immunity following parenteral inoculation of mice with virus preparations has been closely studied. Inasmuch as massive doses of living virus have to be given intraperitoneally (Rickard and Francis, 1938) in order to produce infection of the lungs by this route, the results of parenteral inoculation with living or with inactivated (formolized) virus are rather similar. Antibodies are most rapidly produced, however, after the introduction of living virus intraperitoneally, and persist somewhat longer than when inactivated virus is used (Oakley and Warrack, 1940). The results of repeated inoculation with either virus preparation are better than those of a single dose. The influence of the subtle changes of past infection in mice is well illustrated by the fact that although antibodies to heterologous strains of virus A are poorly developed after either parenteral or nasal introduction of virus, the immunity to heterologous virus following parenteral immunization is much more feeble than that following actual infection. Eaton and Pearson (1940) noted that about 10 times as much virus was needed to protect against heterologous strains as against homologous ones after intraperitoneal immunization either by living or by inactivated virus. Eaton (1940) also estimated that, given by the same route—that is, intraperitoneally—about 30 times as much inactive virus was needed to produce the same degree of immunity as active virus. The importance of the amount of actual antigen in the production of an immunity which is broadly based and effective against heterologous strains is thus clear. The superiority of immunization based on an actual infection, even if this is inapparent, is also obvious. Two further factors have been shown to operate adversely in the case of parenteral immunization. The presence of foreign protein from the host species used to prepare the vaccine has an interfering action on the effect of the vaccine in stimulating antibody formation, and the intraperitoneal route of inoculation is more favourable than the subcutaneous one (Andrewes and Smith, 1939).

Many of these facts which have been elicited from studies with mice have a bearing on human immunization, as we shall see later. Meanwhile, it is necessary to mention the effectiveness of prophylactic administration of immune serum, either from convalescent ferrets or from hyperimmunized rabbits or horses, in the influenza virus infection in mice. Laidlaw, Smith, Andrewes, and Dunkin in 1935 showed that serum given intraperitoneally saved life and diminished the extent of lung lesions if given either before or after intranasal infection. More recently, others (Henle, Stokes, and Shaw, 1941 ; Taylor, 1941b) showed that the serum was much more effective as a prophylactic if given intranasally, and that some effect was demonstrable even up to 10 days after serum introduced by this route. Trial of the method in ferrets has not, however, given results comparable to those obtained in mice (Zellat and Henle, 1941). Unpublished experiments of Glover and Andrewes, to which I am kindly allowed to refer, indicated that some protection could be given to the lung of a ferret, but that it was not possible to protect the nose by inhalation of atomized serum or by exposure to a coarse spray. The intensity of the infecting dose of atomized virus to which the serum-treated ferrets were exposed was carefully controlled, and even a low degree of immunity was unlikely to have been overlooked.

Immunity in Man

(a) Natural Immunity

At least three mechanisms are now known to be concerned in determining resistance or susceptibility in man to influenza virus infection. The first—namely, the development of antibodies with specific neutralizing power for the virus—has been most studied. The distribution of antibodies to virus A in the population in interepidemic times has been found to be related to age. Children other than newborn babies have least, and adults of middle age have most, antibodies. Cyclical changes in the general level of antibodies in the serum are correlated with the occurrence of human epidemics in that levels are highest immediately after an epidemic and lowest before an outbreak, while the individuals with the highest levels after infection undergo the greatest proportional change with the passage of time. Some individuals, particularly those in the middle range of antibody levels, possess remarkably stable antibody titre over periods of many months. Complement-fixing antibodies also undergo cyclical changes, but are at their highest levels for a shorter period of time after an epidemic than are neutralizing antibodies. The fact that sharp changes in titre of antibodies accompanied actual infection and that both clinical and subclinical attacks are associated with changes of a similar magnitude has already been mentioned. So far virus has only rarely been recovered from clinical influenza unaccompanied by serological changes (Adams, Thigpen, and Rickard, 1944), but it is known from deliberate infection experiments that clinical symptoms can at times occur without serological alteration, and the significance of the varying percentage of cases in the various outbreaks which yield neither virus nor antibody change (influenza Y) can be interpreted in various ways, as previously pointed out. Apart altogether from diagnosis, however, the antibody changes during infection are of considerable importance in relation to susceptibility or resistance to attack. All observers are agreed that a majority of cases of influenza are drawn from the population group which has the lowest levels of antibody before infection, but that individuals with all levels of antibody yield cases during an outbreak.

The accumulation of all this mass of information has been the work of many observers in all parts of the world, and evidence on which these statements are made was fully reviewed by Burnet and Clark in 1942. Our own slender contributions may be referred to briefly. In 1936 Andrewes and I bled a group of 50 medical students at St. Bartholomew's Hospital, estimated their neutralizing antibodies, and then observed the experience of this group during the 1937 epidemic. Cases were scattered through all the various levels of pre-epidemic antibody content, and though we did not prove virus A infection in all cases, the uniformity of experience in this outbreak indicated the probability of this diagnosis. A large number of cases of influenza B were observed in 1943 and investigated by Hirst's test. There was a fairly marked scatter of cases (Chart VII), with antibodies during the acute febrile stage at very different levels. Also, the number of B cases was proportionately greater in those with low antibody level in the first specimen of serum. The influenza Y cases whose antibody level showed no change had on the whole higher levels of antibody than the B cases, but some cases had low levels. The correlation between the actual multiplication of antibody content in the blood of the B cases and the original content of antibody was definite, and has been noted by other observers in both influenza A and B (Chart VIII). It means, as Hirst and others (1942) have pointed out, that the same total quantity of antibody is added to the serum of the various cases, and that this is many times the amount already present in those with low levels and is relatively less in those with high pre-existing levels of antibody. Comparison between severity of clinical infection and pre-existing antibody level or degree of multiplication of antibody failed to show any relationship either in virus B influenza (Chart IX) or in virus A influenza (Chart X). This agrees with the known fact that an individual can have a subclinical attack or a clinical infection at any pre-existing level of antibody.

One last fact which must be mentioned concerning the antibody response to infection is the degree of change in the serum for heterologous strains of virus. There has been some controversy between various workers as to whether humans respond to infection with antigenically distinct types of virus with the same degree of specificity for homologous strains as does the ferret. The balance of evidence now favours the view that the amount of antibody in the serum in the acute stage is less when tested against the homologous virus than when

heterologous virus is used. The actual amount of increase in antibody is also greater for antigenically related than for antigenically distant strains of virus, as our own results (Andrewes, Smith, and Stuart-Harris, 1938) indicated. Magill and Sugg (1944) have recently re-emphasized the importance of this finding in connexion with diagnosis. The existence of a multiplicity of antigenic types of the same major strains during any one outbreak, such as has actually been proved, must also have an important influence on the effectiveness of the resistance of the individual whose antibody titre may be adequate to produce immunity against some but not against other types of virus.

The results obtained from study of human infection indicate that no critical level of antibody exists below which there is susceptibility and above which there is resistance to infection as was thought originally (Hoyle and Fairbrother, 1937; Francis *et al.*, 1937). Burnet (1944) has recently emphasized that the fundamental fact concerning immunity to influenza is that in all recent epidemics never more than 50%, and usually under 20%, of the population experience clinical attacks during an outbreak. It has been shown that cases of actual clinical infection are chiefly drawn from individuals with the lower levels of antibody (Rickard, Lennette, and Horsfall, 1940), but that cases can occur throughout the range of antibodies. Yet the 70-odd% of the population which escapes influenza must include many individuals with low antibody levels, though during the outbreak some—perhaps in widespread epidemics the majority—develop increase in antibodies irrespective of clinical attacks. It is in these individuals that the explanation of antibodies as the chief factor in the resistance to infection breaks down. To what, in fact, do they owe their immunity? Doubtless some escape contact with the virus altogether, but this does not account for those who develop subclinical attacks.

Studies of groups of individuals who have been deliberately infected by spraying with virus A or by inhalation of atomized virus A have given much clearer correlation between antibody levels and immunity than the experience during natural infection (Burnet and Foley, 1940; Henle, Henle, and Stokes, 1943). It appears that standardization of the dose of infection produces clinical attacks only in those individuals with low antibodies in their blood before infection. In the experiments of these workers, 26% and 36% respectively of normal individuals experienced clinical attacks and more developed subclinical infection. In the much more intense exposure to virus B by Francis and others (1944), when clinical attacks were produced in 90% of individuals by inhalation of atomized virus, there was much less correlation with antibody levels. Four months after the original spraying Francis could again produce clinical attacks in 90% of the group sprayed initially, in spite of the fact that they still had an enhanced antibody level as a result of their initial experience. Possession of good antibodies was somewhat correlated, however, with shorter and milder fever. Besides demonstrating the evanescence of human immunity to actual infection by influenza virus, Francis thus showed that the defence against infection could be broken down if the intensity of the infecting dose was sufficiently great. We may perhaps deduce that the intensity of

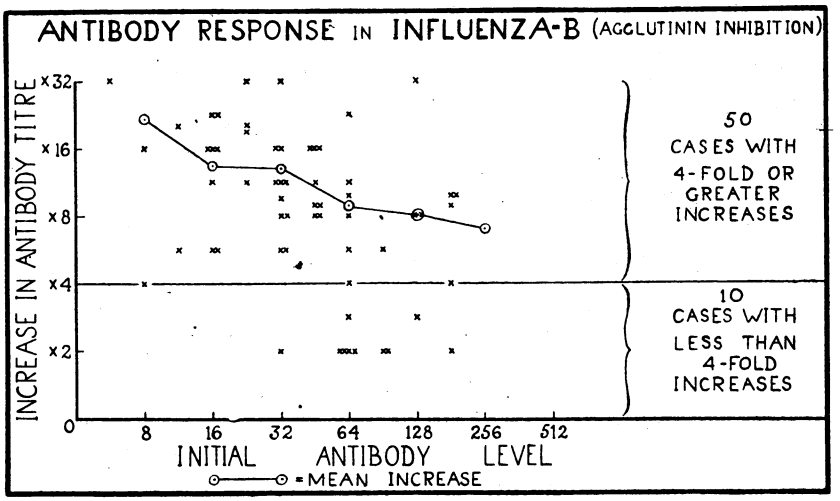

CHART VIII

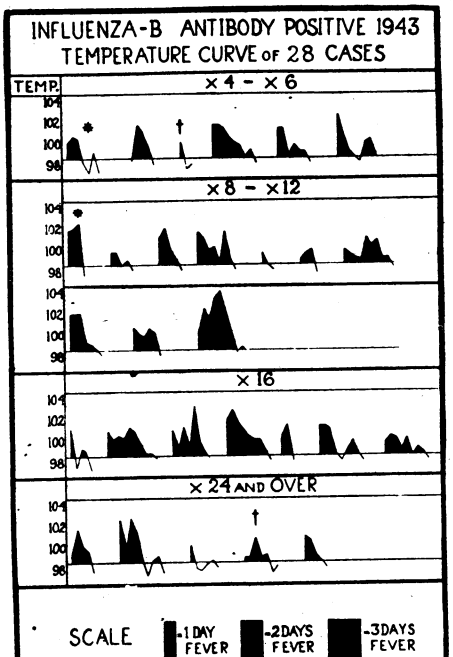

CHART IX.—* Two cases with high initial titre. † Two cases with low initial titre. × 4, etc., indicates the increase in antibody titre (Hirst test).

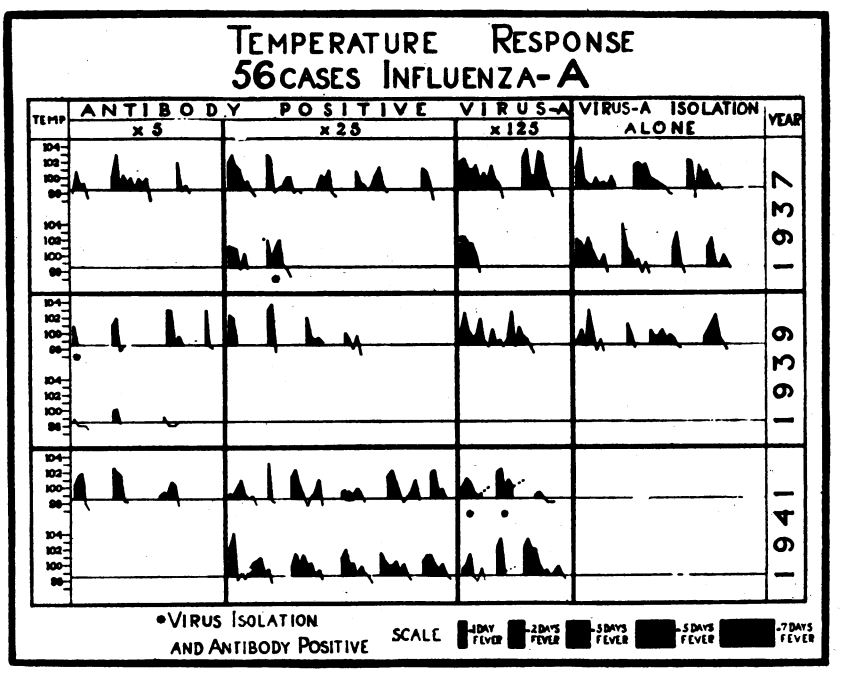

CHART X.—× 5, etc., indicates the increase in antibody titre (mouse neutralization test).

natural infection during an epidemic is much less than that used by Francis and probably less than that of the earlier workers with virus A, in view of the lower percentage incidence of infection observed during natural outbreaks. May it be that repeated exposure to infection during an epidemic breaks down in some individuals the resistance conferred by a high antibody level? Also, may the escape from clinical attack by some individuals with low antibodies be attributed to the fact that they are lucky in receiving just enough virus to cause a subclinical but not enough to cause an overt infection? Other mechanisms governing resistance probably do exist, however, and one of these is the natural defence of the nasal mucosa to attack.

No observations on the changes in the nasal mucosa which accompany human influenza appear to have been made, but a humoral system of defence based on the property of virus inactivation possessed by nasal secretion has been studied both by Burnet and his co-workers (1939) and by Francis (1941). Controversy still exists as to the nature of this substance, which has a wide range of activity against viruses other than influenza. However, different individuals possess different amounts of it, and Francis showed that there was a correlation between the inhibitory activity of the nasal secretion to influenza virus and the influenza antibody present in the blood, and a sharp increase in virus-inactivating power of nasal secretion accompanied infection (Francis and Brightman, 1941). In connexion with this it was also shown (Francis *et al.*, 1943) that an increase in the amount of inhibitory substance in nasal secretion followed subcutaneous immunization accompanied by successful stimulation of antibody production. Burnet, on the other hand, considers the substance to be an enzyme in character, and is inclined now to attribute less significance to its action than at one time (Burnet and Clark, 1942). If, however, both chemical and cellular defence of the nasal mucosa, including the capacity of the nasal epithelium to regenerate rapidly after attack, is considered, it must be obvious that the first line of defence against the virus is probably important. A more doubtful mechanism, which may or may not play a part in the production of clinical phenomena, has been unearthed by Beveridge and Burnet (1944), who studied the skin reactions to inactivated influenza viruses inoculated intradermally. They found that boiled chick allantoic fluid from eggs infected with either virus A or B was capable of eliciting an erythematous skin reaction in both children and adults. No correlation between level of antibody and liability to a positive skin reaction was found, but in children positive reactions were obtained only when possession of some demonstrable antibody suggested past infection or exposure to the virus.

These observations suggested that allergy may be important in determining clinical reaction to influenza virus. Observation on animals has hitherto given little indication that allergic reactions were important. However, Shope and I, in 1938, carried out a few unpublished experiments in which pigs were inoculated intraperitoneally with immune horse or convalescent pig serum and were subsequently inoculated intranasally or exposed to contact infection by swine influenza virus and *Haemophilus influenzae suis*. There was a definite indication that the serum-treated animals were in some way sensitized, because fever and clinical symptoms consistently developed some hours earlier in these animals as compared with the controls who did not receive serum. We were, however, more interested at that time in the possibility of attenuating clinical attacks, and this we failed to accomplish. Allergic reactions in man have been suggested by the deliberate infection experiments of Bull and Burnet (1943), in which symptoms were commoner after intranasal reinoculation than after a first intranasal inoculation with a modified attenuated strain of virus B. An increased incidence of symptoms on reinoculation three to four months after the first spraying of volunteers with the virus occurred in spite of enhanced antibody levels in the serum. The strain of virus used did not produce febrile reactions, and the occurrence of nasal symptoms after both first and second spraying bore no relationship to the subsequent development of an antibody rise in the serum. By the criterion of demonstrable antibody rise, infection was produced in more than 90% of the 23 individuals by the primary inoculation, but in only two instances in the second inoculation. Dissociation of this type between nasal symptoms and immune reaction may be related in some way to the type of infection produced by attenuated viruses, and it was not encountered by Francis (1944) in his reinfection experiments with less modified virus B. Francis, far from demonstrating an increased tendency to symptoms in individuals subject to reinoculation, thought that individuals with the highest antibody titres had less reaction after inhalation of the virus. Time alone will show whether allergy is of much importance in relation to the natural disease.

(b) Artificial Immunization in Man

The discovery of the aetiological agent of human influenza was soon followed by attempts to produce immunity with virus preparations, and these have been actively pursued by several different groups of workers. Emphasis has been largely placed on experiments designed to produce active immunity, and the various workers in this field have concentrated their energies along two distinct lines of attack. British and American investigators have tended to develop methods of immunization based upon the fact that most individuals have, at one time or another, been subject to nasal infection by the virus, and therefore the human problem is essentially one of reinforcing a waned immunity rather than that of developing one in a previously uninfected host. They have therefore tried various methods of immunization by the subcutaneous route, arguing that if a sufficiently intense antibody response could be produced the nasal mucosa could be left to take care of itself. In contrast, Australian workers have concentrated on the development of an attenuated virus strain which could be given intranasally without producing clinical reaction yet producing an effective immunity by reason of its attack on the nasal mucosa, which would be unaffected by subcutaneous inoculation. Such a strain of virus would ideally resemble the yellow fever 17D virus, which has been so successfully used in human immunization against yellow fever (Theiler and Smith, 1937).

Early work in Britain and America was concerned with the demonstration that subcutaneous inoculation of virus enhanced the antibody titres of those inoculated. The fact that inactive formolized virus appeared to be an effective antigen in man was demonstrated at an early date. Furthermore, one inoculation produced as good a rise in antibodies as did several doses. However, detailed study of the factors concerned in determining the relative efficiency of various vaccines in producing antibodies has been chiefly pursued of recent years in America. Hirst, Rickard, Whitman, and Horsfall showed in 1942 that there was a considerable variation in the human antibody response to the same preparation of virus given subcutaneously. The rise in antibodies was correlated with the pre-vaccination titre of the serum, so that the actual amounts of antibody produced by individuals with originally different amounts of antibody were approximately the same as in the case of actual infection. Secondly, the antibody rise induced by subcutaneous vaccination was evanescent and titres had dropped considerably six to nine weeks after vaccination. Thirdly, the antibody response increased in proportion to increase in the amount of virus antigen which was injected. The most concentrated preparations of antigen which were inoculated produced antibody responses of a magnitude similar to those encountered as a result of actual infection. Fourthly, inactive virus, especially in a relatively protein-free medium such as chick allantoic fluid, was as effective an antigen as living virus. The incorporation of a strain of distemper virus originally thought by Horsfall, Lennette, and Rickard (1941) to exert an adjuvant effect on the influenza antigen was not found to be helpful. Bodily and Eaton (1942) added a fifth factor, which would be expected to be of significance if the results of experiments with animals are applicable to man. They compared the specificity of the antibody response following vaccination with that occurring in actual infection with virus A. The sera from vaccinated individuals were more specific in their antibody content to the strain used in the vaccine than were the sera from infected individuals to the infecting strain, although these too showed a limited degree of strain-specificity.

Notwithstanding the apparent drawbacks associated with the use of a virus vaccine subcutaneously, several trials have now been carried out which indicate that such a method of immunization is not only practicable but gives results which

indicate a measure of protection in vaccinated individuals. Our own record in connexion with such studies has hardly been brilliant. In 1937 we employed a formolized vaccine made from filtrates of the lungs of mice infected intranasally with the W.S. strain of virus A—a strain which is apparently particularly specific in antigenic constitution. Only 30 volunteers were vaccinated at an adequate time prior to the 1937 outbreak, and none of these or their controls contracted the disease. Some hundreds of other subjects were also immunized with the same vaccine, but the immunization was too late in the course of the epidemic for reliable data to be obtained. Several instances occurred of influenza A in vaccinated individuals, however, and all the virus strains recovered in the outbreak were relatively remote antigenically from W.S. We wondered if the antigenic difference between vaccinating and infecting strains was the cause of the poor result.

In 1938 we immunized 500 boys at the Naval training school at Shotley in November and December, some with a polyvalent formolized mouse-lung vaccine containing the broadly antigenic P.R.8 strain and also the W.S. strain, and some with W.S. virus vaccine only. When influenza broke out in Jan., 1939, it did not affect this particular institution. A small wave of mild influenza occurred in April, however, and we were able to recover influenza virus A from some of the cases. During the fortnight when virus A influenza was affecting the unit, 4.35% of the vaccinated and 5.4% of the controls suffered clinical attacks. The differences in incidence in the groups receiving the two vaccines were insignificant. We thought that the interval of four months between vaccination and infection meant that the effects of the vaccine had worn off by the end of this period. It was also surprising that this institution experienced its outbreak of influenza so late in the year, for other areas were affected in February and March. Again, we wondered if the number of vaccinated individuals in the community in these months was proportionately high enough to confer temporary immunity on the whole group.

Since the war we have for various reasons been unable to undertake the manufacture of enough virus vaccine for field trial. However, in 1940 a considerable quantity of the combined formolized virus A and distemper vaccine thought by Horsfall and others (1941) to be such an effective antigen was made available to the Medical Research Council for use in this country. In spite of the relatively poor antibody responses obtained on preliminary trial, we decided in 1942 to utilize the vaccine in a controlled field trial in the Army. Some 12,000 volunteers in the various Home Commands were inoculated and a similar number were set aside as uninoculated controls. The vaccination was completed by Dec., 1941, but no outbreak of influenza occurred at all in the next three months, and such tests as were carried out on sporadic cases of influenza failed to give serological evidence either of influenza A or of influenza B.

Thus we reached no conclusion as to whether this vaccine had been beneficial or not. However, Horsfall, and also Brown and his co-workers (1941), used the same type of vaccine in 1940 on some thousands of individuals, and concluded that a real reduction in the incidence of clinical influenza occurred during a subsequent virus A epidemic. The best results were that a 50% reduction occurred in certain of the vaccinated groups of individuals, but the results in other groups were not so good. Since then Francis and his co-workers have experimented with a type of vaccine produced by utilization of the phenomenon of red-cell agglutination by the virus. Virus is absorbed out from allantoic chick fluid with red cells, eluted, and subsequently resuspended in a smaller volume of fluid. These manœuvres result in a considerable separation of virus from foreign protein, and also in a concentration of virus antigen. Preliminary studies of the efficacy of the vaccine were made by exposing vaccinated individuals to an immunity test with inhalation of atomized virus A of a recently recovered strain (Francis, Salk, Pearson, and Brown, 1944). This strain was not identical serologically with the strain used for preparing the vaccine. It was found that the vaccinated individuals had a lessened febrile response to the infection, and that the effect of the vaccine was most evident two weeks after inoculation and had practically worn off four months later. The test of infection was presumably severe in that 80% of unvaccinated men exposed to a similar inhalation developed fever and 50% had temperatures over 100°.

The vaccine, which contained equal amounts of virus A and virus B, was given a large-scale field trial in 1943 during the virus A outbreak of that year. The report by members of the Commission on Influenza of the United States Army (1944), who undertook the organization of the trial, contained unequivocal evidence of the value of the vaccine under the particular conditions of the test. The percentage incidence of clinical influenza in the various groups of the 6,000 controls varied from 3.38 to 9.06, that for the groups of 6,000 vaccinated individuals from 1.15 to 5.25. The incidence of clinical attacks in the vaccinated groups was lowered on the whole to one-fourth that in the controls, and only two groups had small differences between incidence in vaccinated and that in control individuals. These figures included all cases of clinical influenza and excluded afebrile colds, follicular tonsillitis, and infectious mononucleosis. Though the result of serological analysis of the influenza cases has not yet been reported, the general prevalence of virus A during the outbreak suggests that the majority of cases belonged to influenza A. It also seemed that immunization did not begin to affect incidence—that is, to confer immunity—until at least eight days after the vaccine was given. One point is of great importance in assessing the result of this trial. Immunization was carried out in October and November with one subcutaneous dose, and the outbreaks of influenza began about the middle of November. In at least one area vaccination was begun after the epidemic was in progress, but in general an interval of two to four weeks ensued between vaccination and epidemic. It may well be, therefore, that the extraordinarily successful timing of vaccination, which was in fact a matter of chance, was an important factor in the success of the experiment. The serological response to the vaccine was actually at its peak when the outbreak of influenza occurred. It seems probable that this question of the time interval between vaccination and exposure to infection by the virus is of critical importance is deciding the effectiveness of the immunization. Not only in the case of our own experience at Shotley, but in the comprehensive trials carried out in State institutions by Muckenfuss and his co-workers in New York State (Siegel *et al.*, 1942), no difference in incidence of cases of influenza in vaccinated or control individuals was seen when the epidemic occurred six weeks or more after the vaccination. That a concentrated type of virus vaccine may still have some significant effect for as long as one year after immunization has, however, been demonstrated recently by Hirst, Rickard, and Friedewald (1944).

All these experiences with human immunization were carried out with influenza A, and much less is known concerning influenza B. Eaton and Martin (1942) showed that formolized allantoic fluid containing virus B was an effective antigen as judged by the production of neutralizing antibodies, and some of us feel that virus B is actually more highly antigenic, at any rate in animals, than virus A. Salk, Pearson, Brown, and Martin (1944) tested their formolized concentrated virus A and B vaccine by exposing vaccinated and untreated individuals to inhalation of active virus B. As in the experiment with virus A, a diminished febrile response was observed in the vaccinated individuals compared with the controls, but a higher degree of residual immunity was discernible four months after vaccination than in the case of virus A. No field trial of an influenza B vaccine has yet been reported.

In Australia the work of Burnet and his colleagues upon the production of immunity by the intranasal use of attenuated virus strains has been pursued since 1937, when it was found that prolonged cultivation of a virus A strain (Melbourne) on the chorio-allantoic membrane of the chick resulted in loss of pathogenicity for the ferret and mouse. At the same time the virus, though causing an inapparent infection of the ferret, produced an antibody response in this animal, and it thus seemed possible that the same result would be obtained in man. The work with attenuated strains both of virus A and of virus B given by nasal spray was summarized by Burnet in 1943. The essential difficulty has been to produce strains with the correct level of attenuation for man. If attenuation is carried too far, as in the case of the original Melbourne strain, the virus produces neither clinical nor serological reaction. If attenuation is not carried far enough, clinical reactions follow. Ideally attenuated virus produces good serological responses which are closely correlated with the pre-existing antibody levels to the virus and which occur in about 20 to 30% of individuals. At the same time, clinical reactions are trivial or absent in the majority, and take the form of coryza, slight headache, or malaise in the remainder. This method of immunization was tested by Bull and Burnet (1943) by determining the response to a second spraying some months after an initial inoculation. Virus B was used, and the experiment has already been referred to. Although, by the criterion of antibody response, the sprayed individuals were mostly immune three to six months later, nasal symptoms were actually more frequent after the second spraying, which suggested that such symptoms may have an allergic foundation. Repeated sprayings carried out by Mawson and Swan (1943) with mixtures of attenuated A and B strains further showed that failure to respond by antibody rise to a first inoculation was again noted after a second spraying, thus suggesting that

individual factors in resistance to infection are the cause of the failure to respond in the first place. In the experience of these workers and in that of Burnet and Foley (1940), use of a less attenuated virus strain in such individuals led to actual clinical attacks.

The effect of administration of attenuated virus strains during an actual epidemic was seen in only one unit in 1942. There, though influenza, presumably due to virus A, was actually spreading in the camps, no serious acute reaction followed such as would have suggested that spread from person to person under conditions meteorologically suitable for an epidemic would permit the attenuated virus to regain virulence. Nor, however, was much benefit conferred by the immunization, though the study was not carried out under ideal conditions. A reduction in incidence of influenza from 6.63% in the controls to 4.4% in the immunized individuals was, however, observed (Burnet, 1943). Only further experience will enable full judgment to be passed on the relative merit of this method of immunization compared with the subcutaneous method, but simplicity of production and economy of material make rapid large-scale production of the attenuated vaccine much easier than in the case of the concentrated vaccines needed for subcutaneous immunization. It is also conceivable that the time lag before immunity becomes effective is shorter with intranasal than with subcutaneous vaccines, and therefore in the presence of an outbreak the value of an intranasal vaccine would not necessarily be impaired.

Passive Immunization

I can here do no more than mention the experiments which have been made to confer resistance to influenza by passive immunization of man with serum. Earlier in this lecture I mentioned the use of immune serum intranasally in mice and ferrets, and in man successful use of atomized intranasal serum has been reported from Russia (Smorodintseff, Gulanoff, and Chalkina, 1940). Trial of this method last year by Andrewes and Glover (unpublished experiments) during the virus A outbreak gave inconclusive results because none of the groups in which the method was applied developed a sufficient number of cases of influenza in the non-serum-treated controls after the application of serum to the remainder. It was therefore impossible to draw any conclusions as to the value of the method. Possibly such a method might be of greater value during a pandemic type of influenza with high incidence of pulmonary infection by the virus.

Control of Epidemic Influenza

Rational control of any infectious disease depends on knowledge of the whole cycle of the infection, including the source of the causative agent, its mode of spread, and the factors which underlie natural resistance of the host. In the case of influenza, knowledge is still lacking on many of these points, and particularly on the source of infection and whereabouts of the virus in interepidemic times. Possible methods of control based on the mode of spread have, however, been studied, particularly since the outbreak of war. Andrewes and Glover in 1941 defined the mode of spread of contagion in the case of ferrets infected with virus A and showed that, though distant contagion by fine air-borne droplets was entirely possible, the relatively coarse droplets spread from the mouth and nose, particularly in sneezing, were also of great importance in conveying infection. Human contagion is almost certainly conveyed by true air-borne spread at times, but direct droplet infection from man to man must be important. Dust infection is also possible, as shown by the experiments of Edward (1941) on the resistance of influenza virus to slow drying at room temperatures. The great developments which have taken place in recent years in methods of sterilization of the air were reviewed by Andrewes in 1940 and Stuart Mudd more recently (1944). Air-borne particles of influenza virus have been shown to be capable of destruction by such methods as ultra-violet irradiation (Wells and Brown, 1936), or by germicidal mists or vapours such as hypochlorous acid gas (Edward and Lidwell, 1943) or propylene glycol (Henle and Zellat, 1941). Stokes and Henle (1942) have used propylene glycol vapour in a ward, and have demonstrated that atomized influenza virus released into the air is thereby destroyed.

All these methods may play a definite part in the reduction of air-borne infection in crowded messrooms, air-raid shelters, and places of entertainment. They would inevitably be less successful against the direct spread of coarse droplets over short distances, and, though the wearing of masks would provide ideal barriers against such droplets, experience has shown that people will not readily tolerate such measures. The limitations of physical and chemical methods of introducing barriers to the spread of virus during outbreaks of influenza are therefore considerable. Not much more than a reduction of incidence in particular groups where overcrowding would produce an abnormally high rate can be hoped for so far as the uncomplicated virus infection is concerned. There seems more hope that complications may be reduced in incidence, and in pandemic influenza the value of methods of aerial hygiene would be most definite. I do not propose to elaborate this type of work further, as I have not myself taken part in it. I would, however, point out the fact that, even without special apparatus or knowledge, simple measures of hygiene such as improvement in window ventilation, spacing out of beds, and encouragement of a hygienic attitude towards coughing and sneezing may do much to lower the incidence of infection in disciplined communities such as Army units.

When we turn to survey the problem of control of influenza in general it is obvious that the usefulness of all prophylactic methods is dependent on the particular variety of influenza which it is desired to control. In regard to the type of influenza experienced in recent years, there would be little room for methods which failed to reduce actual incidence though they affected severity or incidence of secondary complication. In the face of an outbreak of influenza of the 1918 type, however, any method which modified the course of infection, even if it failed to prevent it completely, would be of use. Naturally, also, there is, in wartime, increased scope for control measures against influenza in order to effect a reduction in the loss of labour to industry or of time to duty from minor as well as major sickness, and measures which fall short of perfection would be relatively more acceptable now than in times of peace. We have seen the promise held out by methods of artificial immunization in limiting the incidence of infection during an outbreak, and the problem would seem essentially to be the application of the method. In such a periodic disease as influenza we are enormously handicapped by lack of knowledge as to when to expect epidemics. The fact that the methods available for artificial immunization are probably effective for only short periods after inoculation adds further difficulty. It will clearly be useless to immunize unless there is a reasonable probability of an outbreak within the next few weeks or unless the outbreak has already begun in neighbouring areas. Use of a vaccine after an epidemic has begun may not be actually harmful, but, in view of the delay before subcutaneous vaccine exerts an effect, only intranasal virus would then have much chance of success. If we are lucky enough to experience indicator outbreaks during the months preceding an epidemic, as occurred in 1943, then we may be able to apply immunization with benefit, but unfortunately we do not yet know whether such experience is exceptional or not. Should we desist from attempts at immunization because of the argument that we owe our present freedom from a recurrence of pandemic influenza of the worst variety to the regular recurrences of the type of mild influenza which we have been considering? My own view coincides with that of Stuart Mudd (1944), who believes that the dissemination of agents of respiratory disease should be attacked whole-heartedly by all possible methods. On the other hand, there is clearly much room for improvement both in how best to apply vaccines and in their actual composition. An example of possible future developments lies in the recent discovery of Friedewald (1944) that the addition of certain substances—of which a mixture of liquid paraffin, killed human tubercle bacilli, and a lanolin-like absorption base known as falba was the most effective—has an amazing adjuvant effect on the antigenic power of influenza virus, and increases the size and duration of the antibody response to virus given subcutaneously. The application of the methods of aerial sanitation in addition to immunization will certainly be necessary if ever we are faced by a recurrence of pandemic

influenza of the 1918 type; and there is the undoubted possibility, as already mentioned, that the causative organism of such influenza may be entirely different in type or in antigenicity from the viruses so far studied. Faced by a virus of entirely novel antigenic type, it is unlikely that any of our present vaccines would have any beneficial effect at all, and we should probably have to spend our time studying the new agent in the laboratory during the period when it was wreaking its vengeance on ourselves and our fellows. General methods of hygiene as well as the methods of aerial disinfection would be our only prophylactic weapons. The use of quarantine for island communities, as in Australia in 1918, may only postpone the fatal day when the pandemic virus begins to spread among the population; but such postponement, in addition to allowing time for the development of specific methods of attack in the laboratory, might mean that the virus then would be less virulent than if it reached the area at the height of its passage through the population elsewhere.

Conclusion

To summarize: the development of knowledge concerning the mechanism of immunity and of resistance to influenza virus infection has been traced in experimental animals and in man. In animals and in man immunity is found to be a complex process, in which the production of antibodies plays only a part. Other processes, though less well outlined, belong to the innate resistance of the mucosa of the respiratory tract, which appears to possess methods of defence by virtue of the nasal secretion in addition to more definitely cellular activities. Possible ways of producing immunity in animals and in man have been described, and the general problem of control of influenza, particularly by the use of the methods of aerial sterilization, have been mentioned.

No speaker on the subject of influenza has any right to conclude a review such as I have attempted without once again emphasizing the fact that we are so fundamentally ignorant of many of the vital links in the chain of the natural infection that the need for more research on this aspect is still pressing, and must occupy as much of our time as methods of application of knowledge so far gained, or even more.

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The Empire Rheumatism Council was established eight years ago to organize research throughout the British Empire into the causes and means of treatment of rheumatic disease. The annual report for 1944 is signed by the chairman, Lord Horder, who welcomes an intimation from St. James's Palace that the Duke of Gloucester wishes to continue as president during his term as Governor-General of Australia, and that absence over-seas will in no way diminish his Royal Highness's interest in the Council's work. A committee on postgraduate education has been set up, with Sir Adolphe Abrahams as chairman. The report confirms a recent announcement in these columns that the tests so far made with a Russian serum have not justified recommendation of its use; but in view of the high reputation of Soviet medical research the Council proposes, when war conditions permit, to invite the Russian scientist responsible for the treatment to visit this country, or, alternatively, to send a research worker to Moscow to make further investigations. The Council looks forward to great progress in the field of clinical research on rheumatic disease when the establishment of a national chain of treatment centres will enable comprehensive tests under full control conditions to be made for evaluating present means and proposing new means of treatment. The *Annals of the Rheumatic Diseases*, by agreement between the Empire Rheumatism Council and the Council of the British Medical Association, is now published by the B.M.A. at Tavistock Square.